## REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 1, 16, 19-21, 23, 24, 26-34, 44, 45, and 53-58 presently appear in the case and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1, 19, 20, 21, 23, 24, 26-34, 44, 45, and 53-57 have been rejected as being indefinite. Claim 1 is now amended to make clear that the claimed peptide consists of 9 or 10 contiguous amino acid residues and that the non-natural modifications, such as recited in dependent claim 21, do not add to the length of the peptide but rather modifies at least one existing residue in the 9 or 10 residues of the peptide. This rejection is now believed to be obviated.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

The examiner has indicated that peptides consisting of SEQ ID NOs: 35-41 are free of the prior art. Claim 16 is now rewritten in independent form. Accordingly, claims 16 and 53-57, which recite for peptides consisting of SEQ ID NOs: 35-41 are in condition for allowance.

Claims 26-29 and 32-34 remain rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. The examiner states that applicants argue that CTLs have activity against breast cancer and the publication by Carmon

et al. shows that BA-46 stimulated CTLs reduce tumor growth. The examiner further states that these arguments are not persuasive because applicants argue with the limitation, i.e., CTLs, not in the claims and that applicants are reminded that the elected invention is peptides, not CTLs. This rejection is respectfully traversed.

With all due respect to the examiner, it appears that the examiner is not considering how CTLs are formed and is misinterpreting the invention as disclosing peptides that are directly capable of treating cancer.

Claims 26-29 and claims 32-34 are drawn to pharmaceutical compositions and vaccine compositions, respectively, effective to inhibit cancer or cancer metastasis, and comprising as an effective ingredient, at least one peptide as set forth in claim 1, i.e., a peptide which appears in the sequence of Lactadherin (BA-46) promotes effective binding to a MHC class I type molecule so as to elicit a CTL response. As is well-known in the art of immunology, naive T cytotoxic ($T_C$) cells are incapable of killing target cells and are therefore referred to as CTL precursors (CTL-Ps) to denote their functionally immature state. Only upon activation will the CTL-P differentiate into a functional CTL with cytotoxic activity. Activation of CTL-P is initiated when an antigen-specific signal is transmitted by the T-cell receptor (TCR) complex upon recognition of a peptide-class I MHC molecule complex, followed by differentiation of the naive $T_C$ cells into effector CTLs that destroy the specific target cells, namely, the cells presenting

the antigen that elicited the CTLs. In the present case, the peptide is a peptide from a tumor-associated antigen (TAA) and the CTLs elicited by such peptides will destroy tumor cells associated with such TAA. As described in the "Background of the Invention" section of the instant specification at page 2, lines 9-11:

> Cytotoxic T lymphocytes (CTL), directed against peptides presented by MHC class I molecules, constitute powerful effectors of the immune system against tumors...

As would be well understood by those of skill in the art, the present claims are directed to pharmaceutical compositions and vaccines comprising the TAA peptides for inhibiting cancer because the TAA peptides will elicit CTLs that destroy the tumor cells. The examiner's attention is directed to page 8, lines 4-7, of the specification, where it discloses:

> The present invention successfully address the shortcomings of the presently known configurations by providing a novel tumor associated antigen peptide effective in eliciting CTL response which may therefore be effective therapeutic agent to combat cancer.

Example 3 on pages 38-40 of the specification discloses results with seven 9-mer tumor associated antigen peptides (Table 7) which are amino acid sequences of human BA-46 predicted to bind with high affinity to HLA-A2. All peptides bound well to the HhD molecules (chimeric human/murine class I MHC molecules) expressed on RMA-S transfectants (Fig. 13), demonstrating stabilization of cell surface HhD on RMA-A cells by Lactadherin (BA-46). The immunogenicity of the BA-46 peptides is shown in Figs. 14-17; where the anti BA-46 activity of CTL produced in HhD mice, which

were immunized with RMA-S HhD-B7.1 cells loaded with either synthetic BA-46 peptides of SEQ ID Nos 35-41 or with breast carcinoma extracted peptides, is shown in Figs. 14 and 15, respectively. The CTL assays were performed on RMA-S-HhD target cells that were loaded with the BA-46 synthetic peptides. The lysis of target cells loaded with breast tumor extracts versus target cells loaded with normal breast extracts, by CTL induced in HhD mice against tumor peptides or against BA-46 synthetic peptides, is shown in Figs. 16 and 17. On page 40, lines 2-7, it is disclosed that:

> CTL against individual BA-46 peptides showed 30-50% higher activity against breast tumor extract versus normal breast extract, supporting the fact that a preferential activity is obtained against breast tumor TAAs.

These results indicate that BA-46 peptides constitute specific CTL epitope enriched in breast carcinoma and may be considered for immunotherapeutic vaccines. As applicants have previously stated, further support for the important role of the peptides of the invention in the treatment of cancer is found in the applicants' own publication, Carmon et al., *J. Clin. Invest.* 2002, 110, pp. 453-462, that describes the effectiveness of Lactadherin-derived peptides of the invention in inhibiting cancer or cancer metastases in a suitable animal model. This publication describes the ability of these peptides to stimulate CTLs (immunity) in transgenic mice and in human lymphocytes. The CTLs destroy breast carcinoma cells in culture and, when

transferred to nude mice that carry a human breast carcinoma, the tumor growth is inhibited.

Thus, based on the disclosure in the present specification, those of skill in the art would recognize that applicants were in possession of the claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 19-21, 23, 24, 26-34, 44, 45 and 52 remain rejected and the new claims 53 and 54 are also rejected for reason of record under 35 U.S.C. 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The examiner states that applicant argues that Figs. 13-17 as well as Carmon et al teach peptide motif recognized by HLA-A2.1. However this argument is held by the examiner to not be commensurate in scope of claims 1, 19, 20, 21, 23, 44 and 52 because these claims are interpreted as drawn to any 10 or 9 contiguous peptides from Lactadherin (BA-46), not limited to those peptides shown at the figures of the publication and also the claims are not limited to the specific MHC class I type the specification and/or the publication show enablement. Applicants further argue that CTLs made from the peptides reduce tumor volume but the examiner finds this argument is not convincing either because the examiner asserts that applicants argue with the limitation not present in the claims (which limitation applicants assume to be CTLs as set forth in the written

description rejection immediately above). It is the examiner's position that applicants' invention is a pharmaceutical comprising peptides as its main active ingredient and that the specification or the mentioned publication does not show any *in vivo* data showing that tumor volume is decreased when peptides are administered to *in vivo* model. This rejection is respectfully traversed.

Applicants' explanations and comments directed to lack of written description rejection under 35 U.S.C. §112, first paragraph, and regarding the role of the peptides of the present invention in eliciting an immune response mediated by CTLs, which response is directed to the treatment of cancer, are also applicable in response to this enablement rejection and suffice in clarifying that the peptides do not play a direct role (as opposed to the elicited CTLs) in the reduction of tumor-volume.

With regard to the Carmon et al. (2002) publication, applicants wish to emphasize that the results reported therein demonstrate the ability of peptides according to the present invention to stimulate CTL (immunity) in transgenic mice and in human lymphocytes, where the CTLs destroy breast carcinoma cells in culture and, when transferred to nude mice that carry a human breast carcinoma, the tumor growth is inhibited. Accordingly, one of skill in the art is enabled to make and/or use the invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 19-21, 23, 24, 26-34, 44 45 and 52 remain rejected and the new claims 53 and 54 are also rejected for reason of

record under 35 U.S.C. 112 first paragraph, because the examiner states that the specification, while being enabling for SEQ ID NOs: 35-41 being able to complex with HLA-A2, does not reasonably provide enablement for any other Lactadherin-derived peptide fragments capable of specifically being associated with any other MHC molecule. The examiner further states that applicants argue that it is routine to screen which 9-or 10-mer peptides bind to which MHC but this argument is not persuasive because Carmon et al (2002) well after the effective filing date of the instant application discloses that it requires a large quantity of experimentation to determine which peptide work with which MHC. This rejection is respectfully traversed.

Contrary to the examiner's assertion that the specification does not show enablement for the scope of claims 1, 19-21, 23, 44 and 52, as drawn to any 9 or 10 contiguous peptides from Lactadehrin (BA-46), and as previously argued, the specification discloses in the section "Material and Methods", page 24, subsection "Scoring of HLA-A2.1 binding peptides", as follows:

> Protein sequences were screened for MHC binding by a HLA Peptide Binding Predictions software approachable through a worldwide web interface (see also reference 82). This software, based on accumulated data, scores every possible peptide in the protein for possible binding to MHC according to the contribution of every amino acid in the peptide. Theoretical binding scores represent calculated half-life of the HLA-A2.1-peptide complex. (emphasis added)

The peptides predicted to bind with high affinity to the MHC molecule are then synthesized according to the method for

peptide synthesis as disclosed on page 24, first paragraph. Actual binding to HhD of the peptides is measured according to the method of measurement of peptide binding by stabilization of cell surface MHC, disclosed on page 25, first paragraph. Finally, *in vitro* cytotoxicity assays are performed as described on page 25, last paragraph.

As stated before, the seven BA-46 peptides that bind to HLA-A2, shown in Table 7 of the instant specification, are those that have shown a higher affinity using the prediction program described. However, other peptides with a different affinity can be predicted and synthesized or modified and might still be useful for the purpose of the invention. Moreover, by using other available HLA Peptide Binding Prediction software, restriction to other HLA molecules can be carried out and the peptides obtained by running those software can be synthesized or modified and tested, all according to the procedures described in the instant specification.

Regarding the examiner's assertion that the specification enables complexation of peptides of SEQ ID NOs: 35-41 only with HLA-A2.1, the examiner's attention is invited to Example 3 in the specification, which discloses the effective complexation of these peptides to the chimeric MHC class I molecule HhD, comprised of human and murine MHC segments. Thus, the scope of claim 1 is supported and enabled in the present specification.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
ALLEN C. YUN
Registration No. 37,971

ACY:pp
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\EN\Y\YEDA\Eisenbach3\PTO\amd after final OA 6 19 03.doc